Remarks

New claim 142 is added herein and finds support at e.g., page 2, paragraph [0018], line 4.

Rejections under 35 USC 112, first paragraph

Claims 76, 79-82, 90, 91, 99, 100, and 141 are rejected for lacking enablement under 35 U.S.C. 112, first paragraph.

Applicant respectfully disagrees for the following reasons.

1. The claims are directed to a method that involves the step of "introducing into the cell an expression vector encoding a double stranded RNA..." The Office Action asserts that inhibition of target gene expression using double stranded RNA is unpredictable and would require undue experimentation for one of skill in the art to perform such a method. The Office Action cites Fire et al., Caplen et al., and Wianny et al. to support the purported unpredictability in the art. However, in contrast to the claimed method, the prior art that the Examiner relies upon to argue that the art is unpredictable all administer dsRNA *exogenously* to a cell. Accordingly, Applicant believes the Examiner's contention does not apply to the present claims. Much of the perceived unpredictability in the art is due to the interferon response that is generated when dsRNA molecules are administered in the manner used in these references. The invention as aforesaid administers dsRNA by expressing it in a cell (i.e., using an expression vector) and consequently *does not produce an interferon response*. Thus, the presently claimed invention is not subject to unpredictability that may occur upon administering dsRNA exogenously to a cell (i.e., by injection or transfection). Thus, there is no basis for this part of the rejection.

Fire et al., Caplen et al., and Wianny et al. each teach delivering dsRNA by exogenous administration. That is, the dsRNA is produced in vitro and either transfected into a cell or injected directly into an organism. This is contrary to the present invention, that administers dsRNA by expressing the dsRNA in a cell from an *expression vector*.

Fire et al. administers dsRNA to C. elegans by injecting the dsRNA directly into the nematode (see e.g., page 809, column 2, paragraph 5, lines 103 and page 810, column 2, paragraph 4). Thus, the dsRNA is administered exogenously to the nematode cells. Similarly, Caplen et al. administer dsRNA exogenously by transfection into cells that express GFP or CAT from an expression vector (see e.g., page 98, column 1, lines 7-8 and page 103, column 1, paragraph 2, line 21-24). Caplen et al. does not administer the dsRNA by expressing it in the cell, but rather administers the dsRNA exogenously. Wianny et al. administers dsRNA exogenously by injecting dsRNA into a mouse embryo (see e.g., page 74, column 2, paragraph 2-4). Applicants submit that each of the cited references do not teach expressing a dsRNA in a cell, as is required by the invention as presently claimed.

The inventors of the presently claimed invention discovered that this method of expressing dsRNA intracellularly does not induce an interferon response (see e.g., Example 11 beginning at page 21 of the specification), while exogenously administered dsRNA that was transcribed in vitro prior to transfection into cells induced such an RNA stress response (see e.g., page 22, paragraph [0190], lines 18-20 and page 22, paragraph [0186], lines 14-16). Thus, expression of dsRNA within a cell as presently claimed overcomes the purported issues related to the exogenous delivery of dsRNAs (e.g., unpredictability due to the interferon response).

The data from each of the cited references was generated using a mode of administration that is subject to a stress response, which contributes to the unpredictability that the Examiner is highlighting. Until the filing of the present application, it was not recognized that the interferon stress response could be minimized by optimizing the delivery of a dsRNA through the use of an expression vector. Thus, the arguments presented in the Office Action are applicable only to dsRNA that is administered exogenously, and do not apply to the invention as presently claimed.

To provide further support for the invention as presently claimed-- that is, expressing dsRNA intracellularly avoids the interferon response that is observed when dsRNA is administered exogenously, Applicant submits herewith Exhibit A, Robbins et al., *Nature Biotechnology* 24(5):566-571 (2006), entitled "Stable expression of shRNAs in human CD34+ progenitor cells can avoid induction of interferon responses to siRNAs in vitro." From the title alone one can see

that the main thrust of this post-filing publication is that expression of shRNAs in cells, in this case even in immune cells, can avoid the induction of interferon responses to siRNAs. That is, while exogenously delivered siRNAs induced an interferon response, the same sequences when expressed in the cell did not stimulate such a response. See, for example, the Abstract, which states "We show that in this system, lipid-delivered siRNAs are potent inducers of IFNα and type I IFN gene expression, whereas the same sequences when expressed endogenously are nonimmunostimulatory." Thus, the Robbins et al. reference confirms the results of the presently claimed invention.

In view of the above, Applicant submits that the invention as presently claimed satisfies the requirements of 35 USC § 112, first paragraph and respectfully requests withdrawal of the rejections and reconsideration of the claims.

2. The Office Action recites the following at page 6, paragraph 2, lines 4-8:

> "Accordingly, due [to] the complexity and unpredictability in the art to RNA molecules that are selective **for in vivo attenuation without inducing a stress response that otherwise produce a stress response when administered in vitro**, would result in an undue burden upon those of ordinary skill in the art beyond the downregulation of PSA expression in human rhabdomyosarcoma cells using the 600 nt expression cassette."

Applicant respectfully disagrees.

The rejection as stated shows an apparent misapprehension of the claimed invention. The invention as presently claimed indicates that dsRNA administered to a cell using an *expression vector* does not produce a stress response, while an equivalent dsRNA administered to the cell *exogenously* produces a stress response. The claims do not indicate that the dsRNA produces a stress response when administered *in vitro* and does not produce such a response when administered *in vivo*, as indicated by the above-noted passage from the Office Action. Thus, there is no compelling reason to suggest that it would require undue experimentation to use a dsRNA to inhibit target gene expression *in vitro* or *in vivo*. One of skill in the art would merely need to

express the dsRNA from an expression vector in a cell as described in the specification and presently claimed.

Applicant respectfully requests reconsideration of the claims for the above-described reasons.

Conclusion

In view of the above, all issues raised in the Office Action are addressed herein. Reconsideration of the claims is respectfully requested.

Should any other fees be associated with this submission, the Applicants hereby authorize the Commissioner to charge such fees to Nixon Peabody Deposit Account No. 50-0850. Any overpayments should also be credited to said Deposit Account.

Respectfully submitted,

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/Mark J. FitzGerald/
Mark J. FitzGerald (Reg. No. 45,928)
Attorney for Applicant
NIXON PEABODY LLP
100 Summer Street
Boston, MA 02110
(617) 345-1058